Identification of Compounds for Modulating Dimeric Receptors

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This application is a continuation-in-part of US 09/461,791 filed 12/15/1999, now abandoned.

Field of the Invention

The invention relates to methods of using the three dimensional structure of an intrinsically covalent dimeric receptor, preferably the insulin receptor, to identify test compounds that will interact with the dimeric receptor and modulate its activity. The invention also includes compounds identified using the methods of the invention.

Background of the Invention

Covalent dimeric receptors are found on almost all cells in mammals. These receptors include IR (insulin receptor), IGF-I R (insulin-like growth factor I) and IRR (the insulin receptor-related receptor). In the case of IR, insulin binding to IR is essential for its manifold effects such as glucose homeostasis, increased protein synthesis, growth, and development in mammals. IR belongs to the superfamily of transmembrane receptor TKs that include the monomeric epidermal growth factor receptor (EGFR) and platelet-derived growth factor receptor (PDGFR). In contrast, IR and its homologues IGF-I R and IRR are sub-types of this family that are intrinsic disulfide-linked dimers of two heterodimers of the form $(\alpha\beta)_2$ (1,2). Monomeric receptor TKs are inactive, but are activated by ligand-induced dimerization that results in autophosphorylation. Dimeric IR-like TKs are also inactive, and are activated by ligand binding without further dimerization. Insulin binding to the extracellular domain of IR results in autophosphorylation of specific tyrosines in the cytoplasmic domain to initiate an intracellular signal transduction cascade (3). However, the structural basis for the mechanism of IR activation by extracellular insulin binding has not been elucidated because the quaternary structure of IR was unknown. Only some of the smaller domains have yielded high resolution structural information.

Diabetes may be caused by mutant IR (eg. acanthosis nigrican or leprechaunism. Insulin resistance leading to diabetes or similar symptoms may also occur.). Diseases are also caused by insufficient amounts of IR ligand. For example, in diabetes, the pancreas produces insufficient amounts of insulin. Insulin activates IR and allows cells to absorb and store glucose. In the absence of adequate insulin, glucose accumulates in excessive amounts in the blood (hyperglycemia). The